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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,518	06/20/2003	Choong-Chin Liew	4231/2055	8219

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
06/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/601,518	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2009 and 17 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19-21,23,24,28,29,31,33,34,38,41,43,49,56 and 59-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19-21,23,24,28,29,31,33,34,38,41,43,49,56 and 59-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/2/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The claims have basis in parent applications 10/268730 and 09/477148, and thus have an effective filing date of at least 1/4/00.

2. The examiner was not able to identify basis in the provisional application 60/115,125 for the instantly claimed invention. For example, basis for the limitation that the blood samples have not been fractionated into cell types from subjects was not identified.

3. Applicant states in the remarks filed 3/17/09 that basis for this limitation is inherent in the recitation of "whole blood" on page 3, paragraph starting at line 12, and the recitation "simple blood sample" in the same paragraph on this page. However, this is not persuasive to provide negative basis for the express negative proviso which speaks to how the sample is processed (or in this case is not processed) after the sample is taken but before the detection of mRNA. The provisional is silent as to the processing of the whole blood sample after it is obtained but before mRNA detection occurs during an assay. Thus, as previously noted, priority is granted in this application to the date of the parent application 09/477148.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The rejection of claims 17, 19, 20, 21, 23, 24, 28, 29, 31, 33, 34, 38, 41, 43, 49, 56, 61, 62, and 63 under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of Ralph et al. (WO 98/24935) or Ralph et al. (6190857) is MAINTAINED as set forth in the office action mailed 9/17/08.

Applicant traverses the rejection on three grounds.

(1) The skilled artisan would not have been motivated to combine the cited teachings because the ordinarily skilled artisan would not have considered the cited combination of teachings to enable the claimed invention.

Applicant argues that the teachings of Sharma et al. surrounding the isolation of total blood RNA are not enabling because Sharma et al. only explicitly teach addition of ribonuclease inhibitors after the freeze-thaw cycle, and not prior to freezing the samples. Applicant argues that the prior art teaches that the ordinarily skilled artisan would expect that blood freeze-thaw based methodology would have required addition of a ribonuclease inhibitor prior to the freezing cycle. Applicant cites the prior art reference Kephart et al. to support this position. Applicant is reminded that a patent specification need not teach, and preferably omits what is well known in the art at the time the invention was made (MPEP 2164.01). Here, by applicant's own argument it is settled that it was well known at the time the invention was made that the addition of a ribonuclease inhibitor would have been necessary or at least preferable in the process taught by Sharma et al. The silence of Sharma et al. on this point is not sufficient to establish that the disclosure is not enabling, since this would have been well known in the art at the time the invention was made, and preferably omitted from their specification.

Applicant points out that Sharma et al. do not include any actual performance of a method demonstrating identification of a gene having disease-specific differential expression. A patent applicant need not have actually reduced the invention to practice prior to filing. The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (MPEP 2121 and 2164.02). In this case, evidence that one could have followed the guidance of Sharma et al. to successfully identify differentially expressed marker genes in whole blood is provided in the declaration filed by Sharma et al. during the prosecution of their patent application. The declaration is cited by applicants in their remarks. Applicant points out that the declaration teaches adding ribonuclease inhibitor to whole blood immediately after collection since the blood was collected in tubes containing EDTA. Sharma is indeed silent as to the tubes used to collect blood samples in their example, but this is a process that was routinely practiced at the time the invention was made. The fact that Sharma et al. do not expressly state as much in their patent specification is not evidence that their disclosure was not enabled, because, as noted, it is preferable to omit what is well known in the art at the time the invention was made.

Applicant is applying a higher standard for disclosure by Sharma et al. than is present in the instant application of any of the parents. There is no particular discussion of exactly how the mRNA used for analysis is to be obtained in the methods disclosed in the instant application and parent application. In example 6, applicant states "A drop of blood was extracted to obtain RNA..." In example 9, applicant teaches that mRNA amplification was from 1 pg of total RNA sample, but is silent as to the steps used to isolate the mRNA. These disclosures have not been cited as being lacking adequate guidance for enablement of the claimed methods, because, the

claims and the specification must be read in light of the state of the art at the time the invention was made. At the time the invention was made, methods for isolating total mRNA from fresh or frozen samples were routine, this is not the invention in the instant case, nor was it so with Sharma. A prior art reference provides an enabling disclosure and thus anticipates a claimed invention if the reference describes the claimed invention in sufficient detail to enable a person of ordinary skill in the art to carry out the claimed invention; "proof of efficacy is not required for a prior art reference to be enabling..." MPEP 2121 (III). At issue here is whether or not one could have practiced the method taught by Sharma et al. successfully without undue experimentation. Since the need to add ribonuclease to the sample prior to freezing was known in the art, and since methods for doing so were routinely practiced, it is concluded that the disclosure of Sharma et al. is enabling.

Thus, applicant's argument has been considered and is not persuasive.

(2) There would have been no reasonable expectation of success in practicing the claimed invention when combining the cited teachings.

Applicant states that at the time the invention was made there was a "paradigm" for RT-PCR analysis of disease biomarkers in blood at the time of the invention- namely the analysis of liver cancer via differential expression of the alpha-fetoprotein (afp) in blood. Applicant cites a reference where AFP was detected in fractionated mononuclear cells of six healthy volunteers, and then cites a series of references where the same observation was not made in healthy volunteers when total blood mRNA was analyzed.

First, all of the references cited by applicant to not support their position or their summary. The claims require detection in "RNA of blood samples that have not been

fractionated into cell types." Matsumura et al. (1994) and (1995) both teach that dextran-saline solution was used to yield an erythrocyte sediment. This is a process where cells are separated by type, namely erythrocytes are separated away from the remaining cells. Thus, neither Matsumura et al. supports the position taken by applicant, and instead they provide examples where AFP was not detected in a blood samples of normal subjects where the blood had been fractionated into cell types prior to RNA extraction.

Applicant provides an abstract of the Liu et al. reference. This abstract states that "mRNA was amplified from total RNA extracted from whole blood." Applicant has provided extensive argument to establish that the phrase "total RNA" does not unambiguously point to RNA from blood samples which have not been fractionated into cell type previously on this record (see remarks filed 6/20/08, particularly pages 8 and 9). Liu et al. cannot be considered, therefore, to unambiguously support applicant's position without further consideration of the entire paper, which has not been provided.

Applicant's review of the literature is selective, not exhaustive. Louha et al. and also attempted to detect AFP expression in the blood of healthy volunteers and failed. Louha et al. teach that mononuclear and tumor cells were isolated using a density gradient. Likewise, Komeda et al. report that they failed to detect AFP mRNA in the blood of healthy controls. Komeda et al. analyzed mRNA from samples that were enriched for mononuclear cells.

Applicant is arguing that one would not have expected to be able to detect expression of marker genes in whole blood versus blood that has been fractionated into cell types, and attempts to use AFP as an example to establish a prevailing paradigm, and therefore that there was not a reasonable expectation of success in practicing the claimed invention. In applicant's argument,

it is critical that Ishikawa et al. were able to detect AFP in blood samples that had been fractionated into cell types, where others had previously failed to detect AFP in blood samples that were not fractionated into cell types. However, as discussed, people had also failed to detect AFP in blood samples of healthy individuals when the blood was fractionated into cell types. Nothing in the text of Ishikawa et al. suggests that they believe that there detection of AFP in healthy controls was due to the method they used to process the blood samples, namely using fractionated blood samples relative to unfractionated blood samples. Applicant's argument that there was a prevailing "paradigm" regarding identifying disease markers in blood samples have not been fractionated into cell types is simply not supported by the facts on the record, since there were also examples of groups who tried to detect AFP in blood samples where cells had been fractionated and failed. The argument is not persuasive.

Absolute predictability is not a requirement in a rejection under 103, only a reasonable expectation of success. The fact that the methods set forth by Sharma et al. did lead to the issuance of a US Patent with claims to the same sets forth a presumption that the methods for identifying differentially expressed markers is in fact enabled. Sharma et al. very clearly teach assaying for disease markers in whole blood, and that the identification of markers would occur by analysis of differential expression. Ralph et al. exemplify a method which is nearly identical to Sharma's except that they use fractionated blood samples. There is no evidence on the record to suggest that the use of total blood RNA as taught by Sharma et al. would have been considered inoperable. Applicant' s argument is not persuasive for the reasons addressed.

(3) The cited combination fails to teach all of the limitations of the claims.

Applicant reiterates the fact that Ralph et al. perform their analysis on fractionated mononuclear cells. This is a piecemeal analysis which does not consider the totality of the rejection. Sharma et al. expressly teach detection in RNA which has not been fractionated into cell types. Applicant states that the examiner is mistaken in her assumption that the RT-PCR step employed by Ralph et al. can be used on the samples taught by Sharma et al. because at the time the invention was made one skilled in the art would not consider analysis of RNA of a blood sample which has not been fractionated into cell types to "correspond" to analysis of fractionated mononuclear cells. Applicant states that these are not the same limitation. It is agreed that these are not the same limitation, as in the two different methods, the isolation of RNA occurs by different methods. Applicant reiterates their argument that the one would not have expected to be able to predictably detect the presence of the RNA detected by Ralph in the blood samples obtained by Sharma et al. Nor does the rejection rely on such an expectation. The rejection merely suggests that following the analysis which is expressly taught by Sharma et al., it would have been obvious to complete an RT-PCR confirmation step, using the same sample type (as logic would dictate to provide adequate control) to confirm the validity of identified markers.

Applicant further returns to the argument that at the time the invention was made, one could not have predicted that whole blood contained a single biomarker, never mind two or more biomarkers for any disease. However, this is not persuasive, as Sharma et al. expressly teach that this can be accomplished. The reasons why Sharma et al. is considered an enabling reference have been previously discussed. There was also extensive discussion in the prior art as to why total blood RNA isolation methods were preferable to fractionated blood samples. For example,

Kruse et al. teach that preparation of RNA from whole blood much more resembles physiological conditions than RNA from purified cells and that only a small amount of starting material is required. Chadderton et al. teach that RNA extracted from whole blood are suitable for use in clinically relevant molecular biology applications. MacFarlane et al. teach that compared with methods that require prior isolation of leukocytes or pathogens from blood, isolating RNA from blood directly increases the feasibility of using RNA-based diagnosis. Thus, contrary to applicant's assertion, it appears that one of skill in the art would have considered total blood RNA to be an appropriate source for an assay that is designed to identify markers for disease.

Applicant points out that the office has a burden of making a prima facie case of obviousness at the time of the invention, and for the reasons set forth in this argument, the office maintains that this burden has been met. Thus, having carefully considered all of applicant's arguments, the rejection is maintained.

6. The rejection of claims 17, 20, 23, 28-29, 33-34, 41, 43, 49, and 59-63 under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of Lockhart et al. is MAINTAINED as set forth in the office action mailed 9/17/08.

Applicant states that the combination fails to render the claims obvious on the grounds set forth above in response to the rejection under Sharma et al. in view of Ralph et al. These have been addressed and were not found persuasive.

Applicant states that RT-PCR is a significantly more sensitive method than the microarray method taught by Lockhart et al. This statement is an attorney argument which is not

substantiated on the record. Further, at the time the invention was made, it was widely known that both methods were able to be optimized to increase or decrease sensitivity. There is no evidence on the record to suggest that once markers were identified by differential display that their differential expression could not be confirmed using a microarray analysis. The rejection is maintained.

In the section addressing this rejection, applicant provides a discussion of Wei et al. (page 20 of the response). This discussion is not germane to this rejection as Wei et al. is not cited in this rejection. The argument is addressed later in the office action where it is more relevant.

7. The rejection of Claim 59 under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of either Ralph et al. as applied to claims 17 and 19 above, and further in view of Wei et al. is MAINTAINED as set forth in the office action mailed 9/17/08.

8. The rejection of Claim 59 under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of Lockhart et al. as applied to claim 17 above, and further in view of Wei et al. is MAINTAINED as set forth in the office action mailed 9/17/08.

Applicant argues that there is no substantive basis to the assertion that one could have reliably predicted at the time the invention was that one marker for diabetes could be found in a blood sample as required by the claims, let alone more than one. The examiner maintains that it is the express teaching of Sharma et al. that from the time a body becomes diseased, a global change occurs, and that markers of this change can be detected in the blood. Sharma et al. was one of skill in the art who believed that multiple biomarkers could be detected in whole blood.

The teachings of Sharma et al. are considered enabled for all of the reasons discussed in this office action. The rejection is maintained.

9. The rejection of claim 60 under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of either Ralph et al. as applied to claims 17 and 19 above, and further in view of Kasuga et al. is MAINTAINED as set forth in the office action mailed 9/17/08.

10. The rejection of claim 60 under 35 U.S.C. 103(a) as being unpatentable over Sharma et al. in view of Lockhart et al. as applied to claim 17 above, and further in view of Kasuga et al. is MAINTAINED as set forth in the office action mailed 9/17/08.

Applicant's arguments against this rejection are duplicative of those set forth to traverse the previous rejections. They are not persuasive for the same reasons. The rejection is maintained.

Double Patenting

11. The previously set forth rejections for obviousness type double patenting are maintained. Applicant did not provide any arguments particularly traversing these rejections.

Conclusion

12. No claim is allowed.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Tuesday and Wednesday, from 10:00 AM until 5:00 PM, and on Friday from 12:30 PM until 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached by calling (571) 272-0753.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the

problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

June 3, 2009